

PENICILLIN IN THE TREATMENT OF NEUROSYPHILIS*

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Five years ago we presented an investigation on the relative merits of malaria plus tryparsamide, and malaria only, as therapeutic agents for the treatment of neurosyphilis; and a detailed account of the changes in the cerebrospinal fluid after malaria therapy was also given at the same meeting. Since then the advent of penicillin has revolutionized the treatment of neurosyphilis.

We are now presenting three groups of patients treated with penicillin only, penicillin plus malaria, and malaria only respectively. Unfortunately, the group treated with penicillin only is so small that the results cannot be compared with those of the other two groups; it is, therefore, being discussed separately.

Material

(1) Patients

(a) *Patients treated with Penicillin and Penicillin plus Malaria.*—The period under review is from February, 1945, to December, 1947, inclusive. During this time 186 patients in the Mott Clinic received penicillin there and elsewhere. Three of these have been omitted from the investigation on account of exceptional treatment, one having been treated with penicillin and T.A.B., one with penicillin and chemotherapy, and one with penicillin and *B. coli* pyrexia. As these numbers are so small it was not thought worth while to include them.

(b) *Patients treated with Malaria Only.*—The period under review is from January, 1942, to December, 1944, inclusive. During this time 405 patients were admitted. Of these, 112 have been omitted from the investigation on account of insufficient information (e.g., inadequate follow-up, having had malaria prior to admission, and doubtful diagnosis). A further thirteen were subsequently treated with penicillin and were therefore also omitted.

The numbers of patients in each group under investigation were as follows:

Therapy	Males	Females	Total
Penicillin only	19	12	31
Penicillin plus Malaria ..	109	43	152
Malaria only	207	73	280

Further analysis of these figures shows that though the numbers in each group differ considerably, the age incidence and the history of previous antisyphilitic treatment, when ascertained, are much the same. The highest incidence occurs in the decade 41–50 in the penicillin plus malaria and malaria only groups, and in the decade 51–60 in the penicillin only group. If anything, the history of previous antisyphilitic treatment is weighted in favour of the malaria group which shows 42 per cent. of cases, as compared with 31 per cent. in the penicillin plus malaria, and 33 per cent. in the penicillin only group: the absence of any previous antisyphilitic treatment is practically the same, being in the region of 50 per cent. in each group.

(2) *Types of Neurosyphilis.*—These are shown in Table I; in each group the percentage of cases of general paralysis is practically the same (70 per cent. for the penicillin plus malaria and malaria groups, and 74.2 per cent. for the penicillin only group), and that of taboparetics is 10 per cent., 12 per cent., and 3.2 per cent. respectively.

(3) *Duration of Disease before Treatment.*—This is a factor of prognostic importance; the sooner treatment is instituted, the better the recovery. From an analysis, it would appear that the penicillin plus malaria group might have a more favourable prognosis than the malaria only and penicillin only groups, since 43 per cent. of the former received treatment within 6 months, compared with 22 per cent. and 16.1 per cent. in the two latter groups. It is difficult to assess how far these

* Read to the M.S.S.V.D. on April 27, 1951.

TABLE I
TYPES OF NEUROSYPHILIS

Type	Penicillin			Penicillin + Malaria			Malaria		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Asymptomatic ..	—	—	—	—	3	3	7	2	9
Meningovascular ..	—	1	1	4	1	5	8	2	10
General paralysis of the insane ..	13	10	23 (74.2%)	81	30	111 (70%)	140	57	197 (70%)
Taboparesis ..	1	—	1 (3.2%)	11	5	16 (10%)	25	8	33 (12%)
Tabes ..	1	—	1	1	3	4	9	2	11
Optic atrophy (<i>per se</i>)	—	—	—	—	—	—	1	—	1
Mixed ..	—	—	—	8	—	8	8	1	9
Meningovascular + parenchymatous ..	4	1	5	4	1	5	9	1	10
Total ..			31			152			280

factors might influence the results; as is well known, the time of onset is notoriously difficult to judge, and we are left with 30 per cent., 27 per cent., and 38.7 per cent. respectively for whom no definite date could be ascertained.

(4) **Length of Follow-Up.**—The minimum period of follow-up is 6 months and the maximum 3 years, the end being arbitrarily taken as June 30, 1950 (Table II). The malaria treated patients have, of course, been followed up considerably longer, and some of the penicillin only and penicillin plus malaria patients for 4 or even 5 years. The period of comparison has been restricted to 3 years. Patients treated in 1947, of course, can only have been under observation for 3 years, and consequently there is a sudden and increasing drop in numbers in the fourth and fifth years. Patients who died within 6 months of treatment have not been included in Table II.

Treatment

(1) **Penicillin Only.**—Mixed penicillins in aqueous solution were given throughout, except in one case where penicillin in oil-wax was given.

With regard to the frequency of dosage, during most of the period under review patients treated at the Mott Clinic received 300,000 units once daily, which accounts for the relatively high figures under this heading. Towards the end of the period, the dosage was increased to 300,000 units twice daily.

All the Mott Clinic patients were given penicillin intramuscularly. The figures given under "MIXED METHODS" in Table III (overleaf) refer to the relatively few patients who received penicillin intrathecally or intravenously as well as by the more usual intramuscular method.

TABLE II
LENGTH OF FOLLOW-UP

Interval since Treatment	Penicillin			Penicillin + Malaria			Malaria		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
6-11 months ..	1	0	1	5	5	10	14	2	16
12-17 months ..	1	1	2	7	2	9	9	0	9
18-23 months ..	1	0	1	7	2	9	9	2	11
2 years ..	2	3	5	32	18	50	11	2	13
3 years ..	4	3	7	54	14	68	120	56	176

TABLE III
METHOD OF ADMINISTRATION AND PENICILLIN DOSAGE

Administration			Penicillin			Penicillin + Malaria		
			Male	Female	Total	Male	Female	Total
Method	..	Intramuscular ..	18	12	30	97	43	140
		Intravenous ..	0	0	0	2	0	2
		Intrathecal ..	1	0	1	1	0	1
		Mixed ..	1	0	1	1	0	1
		No details ..	1	0	1	10	0	10
Dosage	Frequency	Once daily ..	12	8	20	75	28	103
		Twice daily ..	2	3	5	8	4	12
		Round the clock	4	1	5	13	10	23
		No details ..	1	0	1	13	1	14
	Amount	Below 4 million ..	2	0	2	10	6	16
		4-12 million ..	15	12	27	89	35	124
		13-20 million ..	2	0	2	4	0	4
		Over 20 million ..	0	0	0	3	2	5
		No total given ..	0	0	0	3	0	3

TABLE IV
MALARIA PEAKS

Malaria Peaks (103°F. or Over)				Malaria			Penicillin + Malaria		
				Male	Female	Total	Male	Female	Total
0-6	40	11	51	31	13	44
7-12	127	51	178	71	29	100
More than 12	40	11	51	7	1	8

With regard to the total dosage, all the Mott Clinic patients had either 4.2 or 8.4 million units in a period of 14 days. The details of penicillin dosage and administration are shown in Table III.

(2) **Malaria.**—Table IV shows the number of peaks of fever of 103° F. or over given by malaria.

Results

(1) CLINICAL

(a) **General.**—Table V shows the clinical results. The asymptomatic cases are omitted, since by definition they cannot "recover clinically", success or failure being judged by whether or not in the course of time symptomatic neurosyphilis develops, and by the progress of the cerebrospinal fluid.

The figures under the heading "DEATH" refer only to those cases in which death was directly due to neurosyphilis. Deaths due to intercurrent disease or accident are omitted.

The most striking feature of Table V is the great difference in the death rate between the penicillin plus malaria and the malaria only groups. (The

figures for the penicillin group are not comparable, for reasons which will be explained later, and must therefore be ignored.)

In 3 years, 31 per cent. of the malaria group and only 13.5 per cent. of the penicillin plus malaria group died of the disease. This seems to correlate with the malaria, malaria-tryparsamide investigation, in which the peak death rate occurred in the third year and was markedly in favour of malaria plus tryparsamide. To express this in another way, at the end of 3 years, of the penicillin and malaria group, 86.5 per cent. were alive, whereas of the cases treated with malaria alone only 69 per cent. were alive.

In comparing the "recovery" rates, it is probably more scientifically accurate to combine the "recoveries" and the "improvements". Whether recovery or improvement occurs depends upon the stage of the disease at which treatment is instituted. Stationary improvement is just as much an indication of the arrest of the disease process as complete recovery. The difference in the recovery plus improvement rates in the two groups, penicillin

TABLE V
CLINICAL RESULTS

Clinical Results	Penicillin			Penicillin + Malaria				Malaria			
	Male	Female	Total	Male	Female	Total		Male	Female	Total	
						No.	%			No.	%
Recovery	3	1	4	27	12	39	27.8	52	19	71	28.5
Improvement ..	4	3	7	40	13	53	37.5	51	26	77	31
No change	1	2	3	23	7	30	21.2	13	11	24	9.5
Death	9	6	15	12	7	19	13.5	65	12	77	31
Relapse	0	0	0	0	0	0	—	3	0	3	—

TABLE VI
DEATHS WITHIN ONE MONTH OF TREATMENT

Deaths	Penicillin			Penicillin + Malaria			Malaria		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
During treatment	1	0	1	0	0	0	6	2	8
Within one month of treatment	3	0	3	1	1	2	13	8	21

plus malaria and malaria, is not very marked—65 per cent. and 59.5 per cent. respectively—but here again it is in favour of penicillin plus malaria.

The figures under the heading "No Change" are of doubtful significance; some of these people seem eventually to die of their disease, whereas others seem to continue unchanged for at any rate 5 years. It is possible that in the latter group the disease process is arrested, and that they should really be classed with the treatment successes, whereas in the former the disease slowly progresses, the continuing deterioration being masked by the slow rate and possibly satisfactory environmental conditions.

In 3 years only three of the patients treated with malaria relapsed clinically and serologically.

(b) **Death within One Month of Treatment.**—The figures in Table VI refer to all causes of death, whether directly due to neurosyphilis or not.

The one death that occurred during treatment in a case treated with penicillin only was probably due to a Herxheimer reaction.

A male, aged 62, confused, rambling, and in very poor physical condition, was given 300,000 units of penicillin intramuscularly daily. About 48 hours after the first dose, he began having seizures, and these continued

intermittently until he died about 24 hours later without having regained consciousness.

The three deaths in the same group which occurred within a month of treatment were not directly due to neurosyphilis; one died of purulent bronchitis, one of broncho-pneumonia, and one of acute cardiac failure and auricular fibrillation. All these patients were in a poor physical condition before treatment was begun.

The startling difference in the death rate between the penicillin plus malaria and the malaria only groups can probably be partly explained by the fact that since the advent of penicillin those cases which are relatively poor malarial risks are either treated with penicillin alone or given penicillin first, malaria being withheld until their condition has improved.

(c) **Time Interval between Initiation of Treatment and Appearance of First Signs of Clinical Improvement.**—Table VII (overleaf) shows the interval between the initiation of treatment and the appearance of the first signs of clinical improvement. The only significant feature is the difference between the figures for the penicillin plus malaria and malaria only groups, under "During Treatment"; 9.7 per cent. penicillin plus malaria patients began to improve during treatment, as against only 5 per cent. of those treated with malaria only.

TABLE VII
TIME OF FIRST SIGN OF CLINICAL IMPROVEMENT

Time since Initiation of Treatment	Penicillin			Penicillin + Malaria				Malaria			
	Male	Female	Total	Male	Female	Total		Male	Female	Total	
						No.	%			No.	%
During treatment	3	1	4	8	1	9	9.7	4	4	8	5
Within 1 month	3	1	4	30	16	46	49	47	20	67	43
Within 2 months	1	1	2	4	2	6	6.3	9	3	12	7.5
Within 3 months	1	0	1	1	1	2	2	8	2	10	6.5
Over 3 months	0	1	1	26	5	31	33	42	18	60	38

(2) SEROLOGICAL

(a) **Blood.**—The advent of penicillin appears to have made no difference as regards the reaction of the blood in late neurosyphilis. As before, some specimens became negative quite quickly, and others after a long lapse of time, while yet others remained apparently persistently positive.

(b) **Cerebrospinal Fluid.**—With modern techniques, slight residual abnormalities of the spinal fluid are seen to persist in cases, which, with cruder methods, would be returned as negative. We regard as normal standards the following :

- (i) Cell count 5 cells or less per cmm.
- (ii) Protein content .. 40 mg. per cent. or less
- (iii) Wassermann reaction + 6+ (+ on 0.5 ml.) or under
- (iv) Lange curve no figure greater than 2 on the left, e.g., 2132100000

(i) **Cell Count.**—In all three groups, the cell count becomes normal rapidly and permanently. It is probable that this occurs within about six months of treatment in almost 100 per cent. of patients, the apparent delay in some cases often being due to delay in examining the fluid.

(ii) **Protein Content.**—The behaviour of the protein content of the spinal fluid has caused us some perplexity. At the end of 3 years, 81 (65 per cent.) of the 125 fluids examined in the penicillin plus malaria group, and 131 (63 per cent.) of the 209 fluids examined in the malaria only series, had a normal protein level. But 22 (17.5 per cent.) in the penicillin plus malaria group, and 25 (12 per cent.) in the malaria only series, had a persistently raised protein content although all the other constituents had returned to normal. It is not clear why this happens—possibly it is the result of damage to the choroid plexus in the disease process, permitting an excess infiltration of globulins into the cerebrospinal fluid. In our experience, this anomaly is not very uncommon, but we are inclined to disregard it provided the other fluid abnormalities have been restored to normal.

(iii) **Wassermann Reaction.**—In the penicillin plus malaria series, of 128 fluids examined, 95 (74 per cent.) had a negative Wassermann reaction at the end of 3 years. Of these, 74 (78 per cent.) had become negative 12 months after treatment. In the malaria only group, of 211 fluids examined, 176 (83.5 per cent.) were negative at the end of 3 years, and of these, 119 (67.5 per cent.) became so in only one year.

(iv) **Lange Curve.**—At the end of three years the Lange curve was negative in 103 (80.5 per cent.) of the 128 fluids examined ; of these 103, 67 (65.0 per cent.) had reverted to normal within a year from treatment. In the malaria group, out of 211 fluids examined, 143 (67.5 per cent.) were negative at the end of three years, 79 (55 per cent.) of these 143 returning to normal in one year after treatment.

(v) **Cerebrospinal Fluid as a Whole.**—As regards the ultimate success or failure in reversing the spinal fluid to normal, the addition of penicillin seems to make very little difference : in our small numbers, 65 per cent. of the penicillin plus malaria cases and 61 per cent. of the malaria only cases were reversed to normal in 3 years.

When an analysis is made of the time taken to produce a negative fluid, it appears that the addition of penicillin speeds up the process, in that 36 per cent. of fluids in penicillin plus malaria cases achieved negativity in 6 months after treatment, as against 25 per cent. of fluids from cases treated with malaria (see Figure, opposite).

(3) PENICILLIN ONLY.

This series is so small and so heavily weighted against success that it is impossible to compare it with the other two groups. Most of the patients who received this treatment were placed in this group because they were in such poor physical condition, hence the high death rate. However, in spite of this handicap, it is possible to present a few general conclusions about results in this group.

(a) **Herxheimer Reaction.**—As there was not always sufficient information available about patients

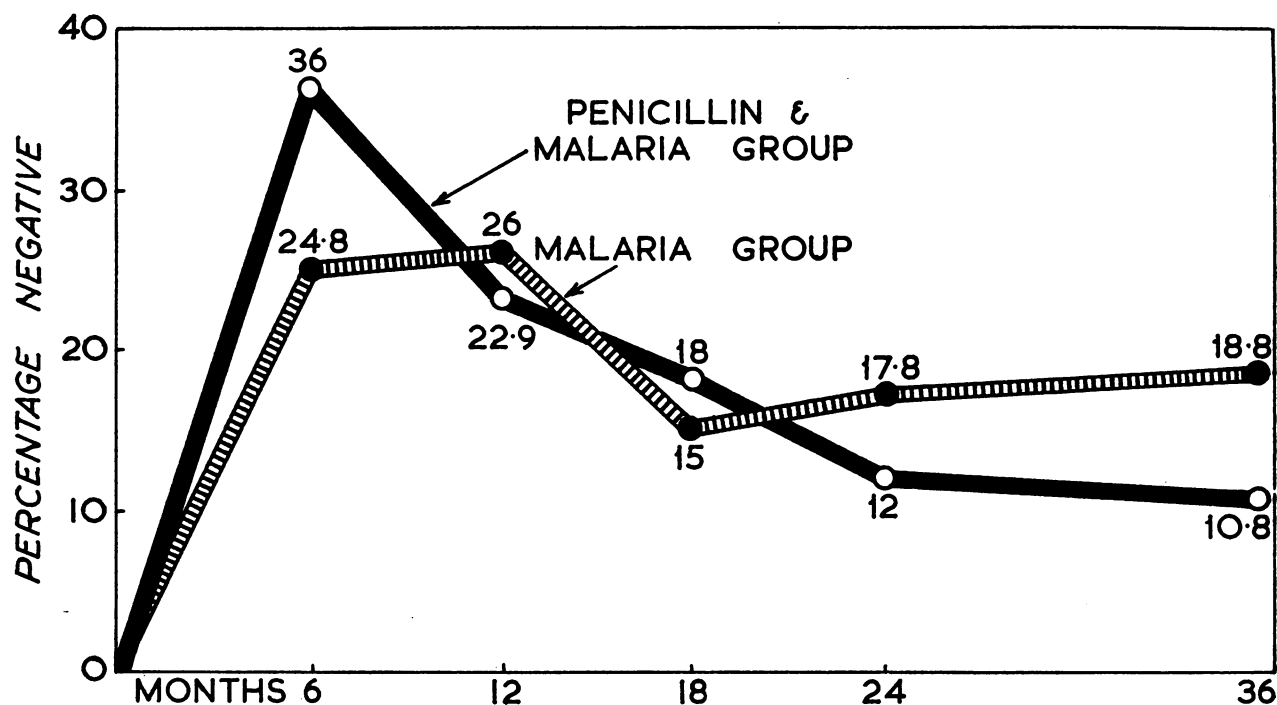


FIGURE.—Time after treatment before cerebrospinal fluid became negative.

treated elsewhere to say whether or not a Herxheimer reaction occurred, only those receiving penicillin in the Mott Clinic and the Maudsley Hospital were investigated from this aspect (Table VIII).

Out of 153 cases there were only four Herxheimer reactions; of these the one fatal case (in the penicillin only group) has already been described.

Of the three that occurred in the penicillin plus malaria group, two were mild febrile reactions, one appearing within a few hours of the first dose and

one 24 hours after. The remaining case was interesting, complex, and dramatic:

The patient was a woman aged 33 years who was depressed and retarded and in very poor general condition. She was put on penicillin 300,000 units intramuscularly twice daily. About 48 hours after the first dose her temperature rose to 99°F. and she did not seem so well. The next day she was much worse with a temperature of 103.4°F. and her mental condition had deteriorated. She was mute, resistive, and refused food. The following day she was slightly better and her temperature began to fall. The day after she was much better and began

TABLE VIII
HERXHEIMER REACTIONS

Herxheimer Reactions	Penicillin			Penicillin + Malaria			Total
	Male	Female	Total	Male	Female	Total	
Patients who had Penicillin at Horton or Maudsley Hospitals	17	9	26	89	38	127	153
Herxheimer Reaction	No	16	9	25	88	36	124
	Yes	1	0	1	1	2	3
							4

taking her food again. On the fifth day she had three epileptiform seizures, from which she made a rapid recovery, and her condition reverted to what it had been on admission.

(b) *Penicillin Failures.*—That penicillin is no more effective than other forms of known treatment in fulminating general paralysis of the insane is illustrated by the following case history :

A male, aged 40, was admitted to the Mott Clinic on December 12, 1945. According to the history he had been quite well until about 10 days before admission when he became strange in manner and slept badly. He made scenes over nothing, and thought he had enormous sums of money, and was going to bring off gigantic business deals. Two days before admission he began to shout and rave, the following day he threw all his clothes out of the wardrobe and said they were to go to the cleaners whether dirty or not, and then ordered a Rolls-Royce to take him out. He became wilder and wilder and finally rushed off to the police station. The police took him to hospital immediately.

On admission he was elated, grandiose, and violent, declaring that he was a lord and owned all the money in the world. His general condition was very poor, with emaciation and pressure marks on both hips. His only physical signs were pupils which were inactive to light, generalized tremors, and an unsteady gait. His blood and cerebrospinal fluid were strongly positive.

He was given 300,000 units of penicillin intramuscularly daily to a total of 4,200,000 units. But in spite of this, he steadily deteriorated and he died on February 26, 1946, 12 weeks after the first appearance of his illness.

(c) *Penicillin Successes.*—In certain cases penicillin brings about an amazingly rapid and probably permanent clinical improvement, which is usually followed by a reversal of the cerebrospinal fluid to normal. The notes of one such case are appended :

A female, aged 54, was admitted to the Maudsley Hospital on January 22, 1946, with a history of 18 months' illness. She had complained of blurred vision, and she wandered about, falling all over the place, and had lost all idea of time.

On admission, she lay in bed rather somnolently, opening and closing her eyes, sometimes muttering to herself. She was grossly confused and disorientated. Her only physical signs were pupils which reacted sluggishly to light, slurred speech, left-sided hemiplegia, and sucking and grasping reflexes. Her blood and cerebrospinal fluid were strongly positive. She received 300,000 units of penicillin intramuscularly daily to a total of 4,200,000 units. Within 3 days, she began to show steady improvement, both mental and physical, which continued unabated until April 13, 1946, when she was discharged. She has maintained her improvement, and although still very simple and childish, is able to manage her housework and shopping under supervision. Her cerebrospinal fluid has become negative.

(d) *Penicillin apparently needing Supplementary Treatment.*—Two cases under this heading may illustrate two aspects of possible penicillin failure :

In the first case, there was an early, rapid and dramatic clinical improvement during the administration of 4.2 mega units of penicillin, but this was not followed by the usual serological improvement. About 11 months after treatment, although the patient's mental improvement was maintained, he was not so well physically and his cerebrospinal fluid was still strongly positive. Had he not died of coronary thrombosis, it is almost certain that he would have received further treatment.

In the second case the picture is reversed ; there was no clinical improvement after penicillin treatment but the patient's cerebrospinal fluid was better although by no means normal 5 months after treatment. Almost immediately after a course of malaria given 5 months after the penicillin, he showed marked mental improvement. This has been maintained and his cerebrospinal fluid has become negative. It could, of course, be justly argued that a second course of penicillin would similarly have improved his condition. The case is of interest, however, in that it does bring to light the difficulty in making a decision regarding a further course of treatment in those cases whose clinical improvement is slow, but in whom the reversal of the abnormal condition of the fluid appears to be progressing satisfactorily.

Discussion

It is a matter for regret that we have been unable to present comparable series of cases treated with penicillin only, penicillin plus malaria, and malaria only. We have, however, presented two long series of penicillin plus malaria and of malaria only. The few cases receiving penicillin only cannot be ignored. We hope it is possible to indicate some significant points and to draw some tentative conclusions.

It seems that in certain cases penicillin alone is adequate and also that in some cases a single course of penicillin is inadequate. We have no evidence that these would respond satisfactorily to a further course of penicillin, but, as would be expected, they do well with malaria.

It cannot be denied that malaria plus penicillin is far more efficient than malaria alone. These results are paralleled by the much better results obtained when malaria is supplemented by chemotherapy. Here we would make an earnest plea that penicillin might well, and indeed should, supersede tryparamide. Ophthalmic catastrophes in connection with pentavalent arsenical therapy continue to occur, and the substitution of penicillin for tryparamide would avert these calamities.

We are justly proud of our follow-up clinic which was started 15 years ago. The personal contact

between the clinic social services and the patient is one to be encouraged. We should welcome some patients previously treated with penicillin only whom we might follow-up. The assessment of the progress of the changes in the cerebrospinal fluid is relatively easy, but the gauging of clinical improvement and the rehabilitation of the patient back to his work and his social environment is difficult, and requires the greatest patience and forbearance on the part of the relatives. We should also like to bring to your notice one of the most distressing sequelae of treatment, that of enuresis (usually nocturnal) in an otherwise physically and mentally recovered patient.

Recent work on the action of penicillin may explain a point in which we have been much interested. We have had good clinical and serological results in spite of having adhered consistently to a once, or at most twice, daily dosage of aqueous sodium penicillin. We have always advocated this regimen as less distressing for the patient and as saving the time of the nursing staff. Eagle (1949) states that penicillin may be administered by any preparation and by any route, so long as it is "repeated sufficiently often and at such intervals that an effective concentration is provided for a sufficient aggregate time to kill all the organisms, and that the penicillin-free interval between injections is less than the time required for the surviving organisms to recover and to resume multiplication". If, as has been established, the multiplication time of *Treponema pallidum* is approximately 30 hours, then the once-daily dosage of penicillin is sufficient. As pointed out by Fleming (1950, 1951):

The laboratory test measures the *bacteriostatic* concentration which, for penicillin, may be well below the *bactericidal* level required to destroy bacteria in infected tissues.

This being the case, it would appear that an initial high level should be aimed at and, provided that the injections are given at the required intervals, this can be better attained by the injection of the sodium salt in an aqueous solution than by a procaine preparation which produces a sustained but low blood level.

In our group of cases, the incidence of Herxheimer reactions has been extremely low, only four out of 153, although in no case was a preliminary course of bismuth given. Purdon Martin (1948) mentioned one possible Herxheimer in his small series, but the Americans report a much higher incidence. Hoenkenga and Farmer (1948) report 34 per cent. febrile responses in 349 patients with various types of neurosyphilis, and state that in general paralysis the incidence rose to 74 per cent., though aggravation

of mental symptoms or neurological signs occurred in only 1.7 per cent. Shaffer and Shenkin (1950) report a fatal case with syphilitic pachyleptomeningitis, who, after the institution of penicillin therapy, developed a severe febrile reaction and died 10 days later. Earle Moore (1949) has suggested that patients, especially general paralytics, might do better if they were started on fever therapy before penicillin, rather than on penicillin before fever therapy, and it is worth noting that in our series the three Herxheimer reactions that occurred in the penicillin plus malaria group were all in patients who received penicillin before malaria. In this connection the work of Bruetsch (1949) is interesting. He maintains that malaria destroys the spirochaetes indirectly, through antibody production resulting from the stimulation of the reticulo-endothelial system. This process, of course, unlike the treponemicidal action of penicillin, takes time.

Dattner (1949, 1950a, b) whose experience in malarial therapy must be considerable, has now come down heavily on the side of penicillin. In a most useful review, he presents the views of various workers, and this mass of literature on penicillin therapy is only evidence of the different opinions that prevail. Curtis, Horne, and Norton (1948) reported that there seemed to be no great difference in the response of patients with most types of neurosyphilis to penicillin alone or to penicillin plus malaria; this was true for all groups except the general paralytics, who showed after 2 years a 16 per cent. superiority in spinal fluid improvement in favour of combined therapy. In a further report by Curtis, Kruse, and Norton (1949), it is stated that in 68 patients with paresis and taboparesis, followed-up for a minimum of 3 years, there was a superiority of only 3 per cent. in spinal fluid improvement in favour of combined therapy. With a long follow-up period they postulate that:

Even in paresis, penicillin alone will prove as effective as penicillin plus malaria.

Curtis, Kruse, and Norton (1950) again checked those patients who had been adequately observed for 1 to 5 years after a single course of treatment. They admit that any of their cases might have received further antibiotic therapy elsewhere and that the results might have been influenced by some patients suffering from milder forms of neurosyphilis in the penicillin alone group. Nevertheless, they feel that definite conclusions can be drawn, and that, taking into account the various types of neurosyphilis as a whole, there is no difference between the results obtained with penicillin alone as compared with penicillin plus malaria. But if the

important group of paresis (plus taboparesis) is assessed separately,

22.7 per cent. attained precipitation-test (Kahn) negativity following penicillin alone in contrast to 40 per cent. treated with combined therapy. This is a significant difference and demonstrates a superiority of penicillin plus malaria, at least in this particular comparison.

Kopp and others (1948) have given a summary of their experience in treating, between 1944 and 1948, 394 patients of whom 77 per cent. were paresics. Penicillin alone was given to 94 patients, and the remainder received penicillin plus half the usually accepted course of malaria. It was concluded that the combined therapy was "equal or superior to any treatment thus far known in late symptomatic neurosyphilis". Re-treatment was necessary in 52 per cent. of the penicillin only group, and even in the penicillin plus malaria series 21 per cent. of patients received further therapy. It may well be that the amount of penicillin used (3 mega units) was insufficient.

Dattner (1949) reports the subsequent history of penicillin failures in neurosyphilis; of 88 cases of general paralysis and taboparesis there were six failures, of whom three were successfully retreated with penicillin, and one half of 43 patients who failed with one course responded favourably to a second course of penicillin given in larger amounts. "So far" he continues "our files contain only three patients who failed even with repeated courses of penicillin. This is most probably due to underdosage of penicillin". A further report (Dattner, 1950, b) records three of these failures; they were all patients with asymptomatic neurosyphilis who, in spite of repeated course of penicillin, continued to show an active disease process, as indicated by the fluid abnormalities. In these patients still higher dosages of penicillin were given with satisfactory results.

There is no doubt, however, that some of these failures are evidence of individual idiosyncrasies. Stokes and others (1949) refer to the "effectiveness of old-line treatment and particularly tryparsamide. . . The chief gains so far seem to have been in the rapidity, ease, and safety with which results are secured by penicillin". This somewhat surprising statement certainly brings into relief some of the problems with which we are all faced. In fact, these authors wisely refer to that tendency to "burn out" an infection and the fortunate patient who has something in his protective mechanism which initiates and accelerates a process of recovery already in existence. They conclude:

It is suggested that penicillin, like the older therapies, tips a balance between patient defence and disease

offence: that the amount of treatment needed to accomplish this is not clearly predictable, even by the spinal fluid type. It varies from individual to individual and requires vigorous and prolonged observational control, including repeated spinal fluid examination for the estimation and the determination of course and outcome.

Conclusion

In spite of these conflicting views, we must try to formulate some future policy regarding the treatment of neurosyphilis. Wagner Jauregg's introduction of malaria therapy in 1917 was a great discovery; in 1922 malaria was first used in Great Britain. Fresh hopes were held out for sufferers from general paralysis, hitherto regarded as a fatal disease, and the study of therapeutic malaria afforded unrivalled opportunities to the malariologist for research in that disease.

It has long been established that while malaria was the chief therapeutic agent, supplementary treatment was needed in the way of chemotherapy. The need to cut treatment down within the limits of efficiency and to relieve the patient of subsequent courses of chemotherapy is one to aim at.

It is the more severe parenchymatous group—general paralysis, taboparesis, and optic atrophy—which needs the most energetic measures. Penicillin has thrown down a serious challenge to malaria. Has the time come, or is our present state of knowledge sufficient, to say that we can replace malaria with its hazards by penicillin or some even more powerful antibiotic? It is our view that, in spite of the divergent opinions quoted above, it would be unwise to eliminate malaria altogether, but at the same time we feel that penicillin has usurped the role played by malaria. Penicillin is now the main line of treatment and malaria the supplementary, at any rate in the more severe forms of parenchymatous neurosyphilis.

We should like to acknowledge the help and co-operation that we have received from the medical staff of numerous hospitals and clinics who have been so kind as to send us reports on some of the patients used in this investigation.

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DISCUSSION

DR. T. E. OSMOND said that he knew from personal experience at Horton how greatly these two authors had contributed to throw light on this subject. He believed that Dr. Nicol was the first in Great Britain to employ on any great scale the combined treatment of malaria plus penicillin in neurosyphilis, and also malaria treatment alone. If he might make an analogy with respect to the combined and the single treatment, it seemed to him that if one had two barrels to one's gun one was more likely to shoot a rabbit than if one had only a single barrel. He did not think that the combined treatment, in any event, could produce worse results than the single, and therefore, if there was no contraindication, it was better to use the combined method.

As to the Herxheimer reaction, he thought that the risk of this reaction was very much less than they had been led to suppose. As to the outcome of treatment, it was all very well to carry out various tests, but what mattered was the clinical improvement of the patient. The patient was not interested in the state of his spinal fluid, but only in what he himself felt. Therefore, in assessing the value of a given form of treatment, he personally would pay far more attention to the clinical improvement than to the state of the cerebrospinal fluid.

DR. G. L. M. McELLIGOTT said that he had been impressed by the concept that the persistence of signs and symptoms in treated general paralysis, notwithstanding improved fluid findings, might in some cases be due to the results of psychological trauma rather than to a continuing infective process. He wondered whether Dr. Nicol had any experience of the treatment of these sequelae by means other than further anti-syphilitic therapy. He referred particularly to electrical convulsive treatment and psychotherapy.

DR. R. LEES said that most of them nowadays saw relatively little G.P.I. He himself saw com-

paratively few cases, and he had formed the impression, perhaps falsely, that it was a rapidly diminishing form of neurosyphilis. The great value of the series of cases which the authors had presented lay in the prolonged observation and follow-up period which had been possible in many of them.

There were one or two points on which he would like some enlightenment. First of all, it struck him that the doses which the authors had administered were, by modern standards, very low, so low that he was surprised that any effect had been achieved. Had they any observations to support the view that very much higher doses of penicillin produced better effects? He had seen cases in which there was no response to small doses, but in which a good therapeutic result was obtained by increasing the dose.

It was his impression that in many of the cases where death occurred within 6 or 12 months after treatment by penicillin, the death was due to cardiovascular syphilis. He had had one or two unfortunate experiences in this respect, and had formed the impression that sometimes the cardiovascular system was not adequately investigated before proceeding with a method of treatment which might produce further and irreparable damage to that system. Juvenile G.P.I., in his own limited experience, had a bad prognosis. He wondered whether Dr. Nicol had observed any lasting and appreciable benefit in the tabetic group, and whether optic atrophy appeared to be arrested in many of the tabetic cases.

DR. R. R. WILLCOX said that Dr. Nicol had certainly earned the title of the leading authority on neurosyphilis in Great Britain, as he had published his results at regular intervals for everybody to see. Yet his series of cases were relatively small and there were accounts from two or three American sources of neurosyphilis treated with penicillin running into over 600 cases. He wished to enquire